Objective: To draw attention to the many cases of Stevens–Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) related to nevirapine detected in a multinational case–control study of SJS and TEN.

Methods: Actively detected cases and matched hospital controls were interviewed for exposure to drugs and other risk factors. Data were analysed with case–control and case-crossover methods.

Results: Between May 1997 and November 1999, a diagnosis of SJS or TEN was established in 246 patients. Eighteen were known to be infected by HIV-1 (7.3%), 15 out of these 18 had been exposed to nevirapine. The reaction began 10–240 days after the introduction of nevirapine (median, 12 days) and all patients had received escalating doses. In 10 patients the reaction occurred with the initial dosage. All but one patients received simultaneously a variety of other antiretroviral agents but no specific drug combination emerged, and nevirapine was the only drug significantly associated with an increased risk of SJS or TEN in HIV-infected persons [odds ratio, 62 (10.4; \(\hat{\lambda}\)) in the case–control analysis; odds ratio, \(\hat{\lambda}\) (2.8; \(\hat{\lambda}\)) in the case-crossover analysis].

Conclusions: In European countries the risk of SJS or TEN in the context of HIV infection appears to be associated with nevirapine. The respect of a lead-in period does not appear to prevent SJS or TEN. Because of the severity of these reactions and the long elimination half-life of nevirapine, we suggest discontinuation of the drug as soon as any eruption occurs.

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Keywords: Adverse drug reaction, nevirapine, reverse transcriptase inhibitors, Stevens–Johnson syndrome, toxic epidermal necrolysis
Introduction

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous disorders characterized by acute skin blisters and mucous membrane erosions. They are severity variants of drug reactions that result in necrosis of the epidermis and other epithelia. According to current definitions [1] the main difference between the two is the extent of skin detachment: < 10% for SJS and > 30% for TEN (Fig. 1).

Because SJS and TEN are very rare, the risk cannot be
evaluated in cohorts of treated patients and case-control studies are considered to be more accurate. To assess the risk of SJS or TEN in the context of drug treatment we have been conducting, since May 1997, a case-control study in Austria, France, Germany, Holland, Italy and Israel (EuroSCAR study). Risks are evaluated by comparing the rates of exposure to drugs between case patients and the controls. We present here the data collected in HIV-infected patients enrolled in that study up to 1 November 1999.

Patients and methods

Cases of SJS and TEN were actively detected through regular contact with a network of relevant facilities at which cases were treated. All cases requiring hospital admission were included. The detection network covered a population of about 120 million.

Cases
Selection criteria were: hospitalization with a diagnosis of SJS or TEN; widespread exanthema with ≥1% detachment; more than one blister; not only acral extension; presence of mucous membrane erosions. Potential cases were interviewed by trained investigators to determine exposure to drugs in the 4 weeks before admission (or before the onset of the disease in cases occurring within a hospital).

Clinical data, clinical photographs (available in 90% of cases) and skin biopsies (available in 70% of cases) of potential cases were reviewed by experts blinded to drug exposure data and who: ascertained potential cases as definite, probable, possible or excluded; classified the cases as SJS (detachment < 10% of the body surface area), overlap SJS–TEN (detachment 10–29%) or TEN (detachment ≥30%); and determined the most probable date of onset (index date). Only patients with a definite or probable diagnosis were included in the study.

Hospital controls
Three hospital controls matched for age and sex were obtained for each case among persons admitted to the same hospital with conditions which were not expected to result from drug use (e.g., trauma, pneumonia, appendicitis, hernia).

Questionnaire
Standardized information was obtained from cases and controls concerning medications, recent infections, demographics and relevant medical history. Data collection on medications used a list of indications (e.g., pain, headache, cough) and a list of trade-names of the main ‘suspect’ drugs.

Analyses
Clinical characteristics and drug exposures before the index date were checked in all patients known to be infected by HIV-1.

Because with standard case-control analysis the crude odds ratio (OR) was ‘infinite’ for nevirapine, we used exact logistic regression, median unbiased estimate calculated according to Hirji et al. [2], and lower limit of the confidence interval according to Thomas [3].

The control group extracted from the general population was not optimal for evaluating drugs only indicated for the treatment of HIV infection. To overcome this limitation we performed a case-crossover analysis. The principle of this analysis is to compare the rate of exposure to a risk factor at different periods of time before the occurrence of an acute event [4,5]. In this study exposures during a ‘case period’ of 7 days before the index date were compared with exposures in a ‘control period’ of 7 days, 3–4 weeks earlier. Therefore each case served as his own matched control. The OR was the ratio of cases exposed during the ‘risk period’ only to cases exposed during the ‘control period’ only. When the ratio was infinite an exact binomial confidence interval was calculated.

Results
Between May 1997 and November 1999 364 potential cases and 874 potential controls were enrolled. A probable or definite diagnosis of SJS or TEN was established in 246 cases. Among them 18 were known to be infected by HIV-1 (7.3%); three with SJS, seven with SJS/TEN overlap and eight with TEN. Two of 18 died as a result of the reaction. Among the 246 SJS and TEN patients 57 died (23%). Because the study was limited to the acute phase of the disease, information on sequelae was not available.

Recent or recurrent herpes was not associated to the reactions (0/18 and 2/18 respectively versus 6% and 24% of controls.)

Exposure to nevirapine was present in 15 out of 18 patients (83%). The other three patients were respectively exposed to: diclofenac alone; fluconazole and mintezol; amoxicilline + clavulanic acid, allopurinol and efavirenz, all introduced recently, plus clonazepam, cotrimoxazole, stavudine and abacavir for longer than 2 months.

The characteristics of the 15 patients exposed to nevirapine are presented in Table 1. They were four women and 11 men aged 21–59 years (median, 35 years), 10 were from France, three were from Ger-
Table 1. Characteristics of patients with Stevens–Johnson syndrome or toxic epidermal necrolysis exposed to nevirapine.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Sex</th>
<th>Country</th>
<th>Diagnosis</th>
<th>Detachment (% of body surface area)</th>
<th>Mucosal involvement</th>
<th>Nevirapine dose at onset of reaction (mg/day)</th>
<th>CD4 cell count (× 10⁶/l)</th>
<th>Other antiretroviral drug(s)</th>
<th>Other relevant exposure(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>35</td>
<td>Male</td>
<td>Germany</td>
<td>TEN</td>
<td>55</td>
<td>O</td>
<td>400</td>
<td>87</td>
<td>Nelfinavir, didanosine</td>
<td>Aspirin, pentamidine</td>
</tr>
<tr>
<td>38</td>
<td>Female</td>
<td>Germany</td>
<td>SJS</td>
<td>4</td>
<td>E, L, O</td>
<td>400</td>
<td>1033</td>
<td>Stavudine, didanosine</td>
<td>Paracetamol</td>
</tr>
<tr>
<td>35</td>
<td>Male</td>
<td>France</td>
<td>TEN</td>
<td>30</td>
<td>L, O, G</td>
<td>200</td>
<td>300</td>
<td>Zidovudine, ritonavir</td>
<td>Cotrimoxazole, azithromycine, zidovudine</td>
</tr>
<tr>
<td>40</td>
<td>Male</td>
<td>France</td>
<td>SJS/TEN</td>
<td>12</td>
<td>L, O, G</td>
<td>400</td>
<td>41</td>
<td>Abacavir, nelfinavir, zalcitabine, zidovudine</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Male</td>
<td>France</td>
<td>SJS/TEN</td>
<td>17</td>
<td>E, L, O, G</td>
<td>200</td>
<td>470</td>
<td>Zidovudine, lamivudine</td>
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</tr>
<tr>
<td>48</td>
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<td>France</td>
<td>SJS</td>
<td>8</td>
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<td>200</td>
<td>500</td>
<td>Stavudine, didanosine</td>
<td></td>
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<tr>
<td>59</td>
<td>Male</td>
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<td>SJS/TEN</td>
<td>13</td>
<td>E, L, O</td>
<td>400</td>
<td>70</td>
<td>Abacavir, didanosine</td>
<td></td>
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<tr>
<td>33</td>
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<td>France</td>
<td>TEN</td>
<td>45</td>
<td>E, L, O, G</td>
<td>200</td>
<td>480</td>
<td>Didanosine, stavudine</td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>Male</td>
<td>France</td>
<td>SJS</td>
<td>5</td>
<td>E, L, O</td>
<td>200</td>
<td>150</td>
<td>Zidovudine, lamivudine</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>Female</td>
<td>France</td>
<td>SJS/TEN</td>
<td>25</td>
<td>E, L, O, G</td>
<td>200</td>
<td>475</td>
<td>Zidovudine, lamivudine</td>
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<tr>
<td>50</td>
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<td>SJS/TEN</td>
<td>28</td>
<td>E, L, O</td>
<td>200</td>
<td>268</td>
<td>Didanosine, stavudine</td>
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<tr>
<td>38</td>
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<td>TEN</td>
<td>32</td>
<td>E, L, O, G</td>
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<td>185</td>
<td>Zidovudine, lamivudine</td>
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<tr>
<td>44</td>
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<td>Italy</td>
<td>SJS/TEN</td>
<td>14</td>
<td>L, O, G</td>
<td>200</td>
<td>4</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>21</td>
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<td>The Netherlands</td>
<td>TEN</td>
<td>31</td>
<td>E, L, O, G</td>
<td>100</td>
<td>778</td>
<td>Zidovudine, indinavir, didanosine</td>
<td></td>
</tr>
</tbody>
</table>

*Time from first intake of nevirapine to onset of erythema (days). A drug name given in italic type indicates long-term (> 2 months) exposure. E, Eyes; L, lips; O, oral mucosa; G, genital mucosa.

Discussion

HIV infection increases the risk of drug eruptions [6]. The introduction of highly active antiretroviral therapy (HAART) reduced the incidence of drug eruptions in HIV-infected patients. However, a recent study by the European Study Group for SJS and TEN in HIV-infected persons found that 7% of patients were affected [7]. A previous case-control study of SJS and TEN in Europe showed that 37% of patients were infected [8]. In HIV-infected patients, nevirapine was associated with a 62% increased risk of SJS or TEN, with a lower value of the 95% confidence interval of 4.1. As no control among the 76 validated was exposed to nevirapine, the OR was in finite, with a median unbiased estimate of 62 and a lower value of the 95% confidence interval of 10.4.

All but one of the 15 patients exposed to nevirapine received other antiretroviral agents, introduced on the same date as nevirapine in 12 cases. No specific drug combination appeared among these associated drugs (stavudine, five; didanosine, five; zidovudine, four; abacavir, two; ritonavir, one; nelvirapine, one). The reaction began 10–240 days after the introduction of nevirapine (median 12 days). All patients had initially received a daily dose of 200 mg (one tablet) according to the recommendation of a lead-in period. For 10 out of 15 patients the reaction began when they were still taking this initial dosage.

As no control among the 76 validated was exposed to nevirapine, the OR was infinite, with a median unbiased estimate of 62 and a lower value of the 95% confidence interval of 10.4. All but one of the 15 patients exposed to nevirapine received other antiretroviral agents, introduced on the same date as nevirapine. Details of the case-crossover analysis are shown in Table 2.
Our data strongly suggest that this persistence of a high risk of SJS or TEN in relation to HIV infection is currently associated with exposure to nevirapine.

The reasons why HIV-infected patients are at increased risk of severe cutaneous reactions are unclear. The mechanisms probably involve drug-specific cytotoxic lymphocytes. Therefore one may suspect that it could be part of an ‘immune restoration syndrome’. We consider this hypothesis to be unlikely as in previous years many cases were related to sulfadiazine treatment of central nervous system toxoplasmosis in profoundly immunosuppressed patients. In addition, if these reactions were related to immune restoration they should be observed with a variety of HAART regimens and not be restricted to those including nevirapine.

A high risk of severe cutaneous reactions had been detected in pre-marketing trials of nevirapine, but the benefits of this new antiretroviral agent were considered to outweigh the risk of SJS or TEN. In addition, it was suggested that the observance of a lead-in period decreased the risk of skin reactions [11,12]. However, in two-thirds of the cases exposed to nevirapine in the present study, the reaction occurred during the period of initial low dosage suggesting that escalating doses did not protect against SJS or TEN.

Whether the administration of systemic corticosteroids in addition to nevirapine during the lead-in period might decrease the rate of cutaneous reactions remains unknown [13,14].

Efavirenz and delavirdine, other non-nucleoside reverse transcriptase inhibitors (NNRTI), were released in Europe a few months after nevirapine. These drugs have not been used in as many people as nevirapine. In France at the end of 1999 about 15% of HAART regimens included nevirapine and 10% included efavirenz (D. Costagliola, French Hospital Database on HIV; personal communication, January 2001). In our study we saw a single case (SJS/TEN overlap) exposed to efavirenz and none exposed to delavirdine. Our data strongly suggest that the risk of SJS or TEN is lower with efavirenz or delavirdine than with nevirapine.

We advise physicians to consider seriously the risk of these life-threatening cutaneous reactions when prescribing a HAART regimen. When nevirapine has advantages over another NNRTI, they must inform their patient of the risk of cutaneous reactions and provide clear guidelines of what to do in the case of skin eruption.

In HIV-infected patients a frequent practice is to ‘treat through’ mild eruptions and to withdraw the suspected drug only if markers of seriousness are present. Derived from accumulated clinical experience with sulfonamides in pneumocystosis, this attitude was justified by a lower effectiveness of alternative treatments and by the short elimination half-life of sulfamethoxazole. Concerning nevirapine a similar recommendation was issued by the European Agency for the Evaluation of Medicinal products: ‘nevirapine must be permanently discontinued in patients developing a serious cutaneous reaction’ (EMEA/11260/00, London 12 April 2000).

Withdrawing a drug with a long half-life when signs of a serious cutaneous reaction are already obvious may be too late. Actually the mortality of patients hospitalized for SJS or TEN was not improved if suspected drugs with long half-lives were withdrawn as soon as a diagnosis of SJS or TEN was made [15].

Considering the high risks of severe cutaneous adverse reactions associated with nevirapine; the long elimination half-life of this drug (25–30 h); and the existence of alternative drugs with lower risk of severe skin reactions, we suggest reconsideration of the ‘treating through’ attitude and recommend withdrawing nevirapine if any cutaneous eruption occurs during the first month of treatment.
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